

20 YEARS OF PROGRESS IN DENGUE HEMORRHAGIC FEVER AND OTHER ARBOVIRAL DISEASES RESEARCH

Sumarmo Poorwo Soedarmo¹, Duane J. Gubler², Subaryono W.¹,
Thomas T. Suroso³, Tatang K. Samsi⁴, M. Masyhur⁵,
Suwardji Haksohusodo⁶, Hansa Wulur⁴, and Gerald B. Jennings⁷

Throughout the 20 year history of U.S. Naval Medical Research Unit No. 2 Detachment (NAMRU), many viruses and viral diseases have been studied. The greatest emphasis has been in the field of arboviruses, specifically dengue virus, chikungunya virus, and Japanese B encephalitis virus. The initial focus of the work was to define the extent of the threat posed by these viruses. Studies were conducted to determine antibody prevalence, and to determine the etiologies of infectious febrile disease in hospitalized patients. Later the work advanced into more specific areas, especially the entomologic and clinical components of these viruses.

Little was known of the incidence or kind of arbovirus infections in Indonesia when NAMRU was established. Previous serological studies had used the cross reactive haemagglutination assay. Green *et al.* in 1973¹ provided convincing serological evidence of infections with chikungunya virus and group B

arboviruses by using the specific virus neutralization assay. These results demonstrated the need for further studies to isolate the causative agent, to describe the epidemiology, and to investigate the clinical features of the associated disease.

DENGUE

The Virus

Serological studies by Van Peenen *et al.* in 1974² substantiated earlier reports describing dengue virus as a cause of febrile illness in Jakarta. The existence of dengue virus in Indonesia then was confirmed through the isolation of the virus³. Studies by Suharyono *et al.* in 1979⁴, showed that all four dengue types were endemic in Jakarta, but that dengue serotype 3 was predominant.

Although dengue serotype 3 was the predominate serotype, it was unclear during the early studies whether there was a relationship between serotype and severity of disease. An

¹ National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia

² Division of Vector-borne Infectious Diseases, CDC, Fort Collins, Colorado, USA

³ Directorate General of Communicable Disease Center, and Environmental Health, Ministry of Health, Republic of Indonesia

⁴ Sumber Waras Hospital, Jakarta

⁵ Regional Health Office, Special Province of Jakarta

⁶ Faculty of Medicine, Gadjah Mada University, Yogyakarta

⁷ U.S. Naval Medical Research Unit No. 2, Jakarta

investigation of a dengue virus epidemic in Bantul⁵ found no relationship between type and severity of disease. That epidemic was in contrast to another epidemic a year later near Bantul⁶. This epidemic was associated with milder illness and few deaths, but again the predominant isolate was dengue serotype 3. Of major interest was the finding of lower viremias in these patients. These data suggested the possible presence of epidemic and endemic strains of dengue virus. The question was further investigated by studying hospitalized dengue hemorrhagic fever (DHF) patients in Jakarta between 1975 and 1978⁷. The authors found no difference in the viremia of mild and severe dengue infections. Current research has continued to find predominantly dengue serotype 3, and still the question persists as to its role in dengue epidemics, especially with regards to the five year cycle of dengue epidemics in Jakarta.

The Vector

Aedes aegypti was the presumed vector of dengue virus, and early work attempted to explain the relationship of the vector to dengue epidemics. Van Peenen *et al.* in 1972⁸ found no direct relationship between abundance of *A. aegypti* and rainy season, while Atmosoedjono *et al.* in 1972⁹ found a shift in man-biting behavior during rainy season towards the afternoon hours. The study of the Bantul epidemic¹⁰, which began shortly after the start of rainy season, incriminated not only *A. aegypti*, but also *A. albopictus*. *A. albopictus* were found breeding outdoors in cut bamboo, and thus were dependent upon the rains for breeding.

Variation in mosquito susceptibility to dengue virus was an important question in dengue research. Nalim *et al.* in 1978¹¹, conducted a longitudinal survey of *A. aegypti* populations in Jakarta, discovering a change in the susceptibility of the mosquito to dengue serotype 2 virus. Gubler *et al.* in 1979¹² found the variation in susceptibility was similar for all four dengue types, but the oral threshold for infection was not the same for the four types - infections were greater with types 2 and 3. These combined findings formed the hypothesis that variation in vector competency may help to explain the distribution and spread of DHF epidemics.

A. aegypti are known to be widely distributed in houses and public facilities in Jakarta. Control measures have primarily focused on fogging and mass spraying. Source reduction of water containers is probably most beneficial, but may be difficult because of the public's superficial knowledge of dengue virus.

The Disease

The clinical description of the dengue virus infection in Indonesia was similar to descriptions elsewhere in Southeast Asia, with two important exceptions. First, Eram *et al.* in 1979¹³, found a lower rate of hepatomegaly than was previously reported from dengue patients in Thailand. Secondly, Sumarmo *et al.* in 1983¹⁴, found that many of their confirmed fatal dengue infections did not conform to WHO criteria, specifically thrombocytopenia with concurrent hemoconcentration. Severe gastrointestinal hemorrhage was the cause of death in 30% of the cases. Sumarmo *et al.* in 1978¹⁵, also presented virologically proven dengue infections

presenting as encephalopathy. Recent clinical observations on DHF at R.S. Sumber Waras have continued to observe these findings, but they have also observed a change in the age distribution of DHF patients. The primary age group admitted to the hospital with DHF is the 5 to 9 year olds. Fortunately, the fatality rate has decreased from 70% in 1969-1972 to 5% since 1980.

The surveillance of human dengue virus infections in Indonesia would not have been possible without the breakthroughs in virus cultivation. The use of the simple and economical mosquito inoculation technique for dengue virus surveillance was pioneered in Indonesia¹⁶. This was followed by the introduction of the *Aedes albopictus* derived C6/36 cell line for virus isolation. Although not as sensitive as mosquito inoculation, the procedure was less complicated and more easily performed in different laboratories. Serological surveillance has been difficult with the hemagglutination-inhibition assay because of cross reactive antibodies. The introduction of the IgM ELISA has been an aid in surveillance and diagnosis of dengue virus because of its specificity and early diagnostic capabilities.

CHIKUNGUNYA VIRUS

Serological evidence for chikungunya virus was described in residents of Jakarta by Green *et al.* in 1973¹. The virus was isolated for the first time in Indonesia during the chikungunya epidemic of 1983¹⁷. The clinical symptoms of the chikungunya infection were similar to those described in other Southeast Asian countries, and reminded Indonesian physicians of other differential diagnoses for hemorrhagic fever cases.

JAPANESE B ENCEPHALITIS VIRUS

The existence of Japanese B encephalitis virus (JEV) in Indonesia was suggested by Koesharjono *et al.* in 1973¹⁸, who found evidence of JEV antibodies in pigs. Further investigations led to the first arbovirus isolation in Indonesia, and confirmed the presence of JEV. The virus was isolated from mosquito pools¹⁹ and subsequently from sentinel pigs²⁰. Despite the presence of JEV, there has been no documented illness in humans residing in Indonesia. Efforts have continued in trying to explain the reasons for this paradox.

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